ISTA Pharmaceuticals

15295 Alton Parkway

Irvine, CA 92618

949) 788-6000

fax 949) 788-6010

www istavision com

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
Room 1061, 5630 Fishers Lane
Rockville, MD 20852

RE: Docket No. 05P-0134 -- Response of ISTA Pharmaceuticals, Inc. To Comments Of Amphastar Pharmaceuticals, Inc. (May 31, 2005)

Dear Sir or Madam,

In this paper, ISTA Pharmaceuticals, Inc. (ISTA) responds to comments submitted to the above-named docket by Amphastar Pharmaceuticals, Inc. (Amphastar). *See* Comments in Opposition to ISTA Pharmaceuticals, Inc. Citizen Petition Concerning Marketing Exclusivity for Vitrase® (hyaluronidase injection) (Docket No. 05P-0134) (May 31, 2005) (Amphastar Comments).

Amphastar's comments were in response to a citizen petition filed April 6, 2005 by ISTA. In that petition, ISTA requested that FDA restore the agency's original determination of three- rather than five-year exclusivity for Vitrase® (NDA 21-640), a proprietary formulation of highly purified ovine hyaluronidase manufactured by ISTA. *See* Citizen Petition Concerning Marketing Exclusivity for Vitrase® (hyaluronidase injection) (Docket No. 05P-0134) (April 6, 2005) (ISTA Petition), at 1. Vitrase was approved for marketing in May 2004 as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Under the statutory provisions governing marketing exclusivity in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 321 *et seq*. (FDCA), a drug manufacturer is eligible for three years of exclusivity if his section 505(b) application includes an "active ingredient (including any ester or salt of the active ingredient)" that "has been approved in another [section 505(b)] application," and if the manufacturer's application contains reports of "new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." *See* 21 U.S.C. § 355(c)(3)(E)(iii), (j)(5)(F)(iii). In its citizen petition, ISTA argued that because Vitrase contains an "active ingredient" that was previously "approved" within the meaning of the FDCA provisions on marketing exclusivity, Vitrase qualifies for three rather than five years of marketing exclusivity. *See id*.

Once three-year exclusivity is granted, FDA cannot make effective the approval of any subsequent abbreviated new drug application (ANDA) or 505(b)(2) application submitted for the same "conditions of approval" as the exclusivity

2005P-0134 C2

holder during a period of three years following the approval of the exclusivity holder's application. *See* 21 U.S.C. § 355(c)(3)(E)(iii), (j)(5)(F)(iii). In its citizen petition, ISTA noted that "Vitrase's three-year exclusivity should have prevented FDA from making effective the approval of the Amphastar NDA [for Amphadase®], which was submitted to FDA prior to the Vitrase approval." *See* ISTA Petition at 8 n.9. In its comments on ISTA's petition, Amphastar argues that if FDA grants ISTA's petition, the restoration of three-year exclusivity "should have no bearing whatsoever on the regulatory status of Amphastar's hyaluronidase product, Amphadase®." *See* Amphastar Comments at 1.

In support of its position, Amphastar makes three closely related arguments that misconstrue the scope and effect of three-year exclusivity. First, Amphastar argues that three-year exclusivity blocks only those subsequent applications that rely on the exclusivity holder's data. *See* Amphastar Comments at 3-9. As set forth in more detail below, this argument is based on a misreading of the FDCA provisions on three-year exclusivity as well as the patent certification provisions at issue in the *King Pharmaceuticals* case. Second, Amphastar argues that the scope of three-year exclusivity should be defined by the "purpose" for which the exclusivity holder's studies were conducted. *See id.* at 9-11. This argument is based on a misunderstanding of the exclusivity protections that apply to supplemental new drug applications (supplemental NDAs) as opposed to NDAs generally.

Finally, Amphastar argues -- based on a narrow and unsupported interpretation of the term "conditions of approval" -- that three-year exclusivity should be limited to blocking applications that contain the same data as were submitted by the exclusivity holder, and that seek approval of the same specific drug product as the exclusivity holder. *See id.* at 11-15. This interpretation is inconsistent with the scope of protection set forth in the statute for three-year exclusivity. Three-year exclusivity is effective against all ANDAs and 505(b)(2) applications for the same "conditions of approval" as the exclusivity holder, not just applications that seek approval of the same product as the exclusivity holder's. In this case, Vitrase's three-year exclusivity should delay the effective date of approval of any hyaluronidase injection product submitted for the same indications as Vitrase.

Three-Year Exclusivity Is Not Limited To Blocking Only Those Applications That Rely On Exclusivity Holder's Data

Amphastar argues that three-year exclusivity blocks only those subsequent applicants that rely on the exclusivity holder's data. *See* Amphastar Comments at 3 (stating that Vitrase's three-year exclusivity would not have blocked Amphadase because "the Amphadase application did not rely on any studies conducted by ISTA"). Amphastar bases this argument on the final clause of the three-year exclusivity provision at FDCA section 505(c)(3)(E)(iii). This final clause specifies that approval of subsequent applications will be blocked for three years "if the investigations described in clause A of subsection (b)(1) [the "full reports of investigations" demonstrating safety and effectiveness] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the

person by or for whom the investigations were conducted." *See* 21 U.S.C. § 355(c)(3)(E)(iii).

Amphastar appears to interpret the final clause quoted above, particularly the phrase "and relied upon by the applicant," to mean that the three-year exclusivity provided in section 505(c)(3)(E)(iii) blocks the approval of subsequent applications only if those applications rely on data originally submitted by the exclusivity holder. *See* Amphastar Comments at 3-4 (quoting statute with emphasis added).

Amphastar's interpretation of the statute is incorrect. As explained below, the clause that Amphastar has highlighted in its argument ("if the investigations . . . relied upon by the applicant . . . were not conducted by or for the applicant") means simply that section 505(c)(3)(E)(iii) provides marketing exclusivity against 505(b)(2) applications -- as opposed to section 505(j)(5)(F)(iii), which provides marketing exclusivity against ANDAs. Amphastar's reliance on the *King Pharmaceuticals* case, and on statements made by FDA in the rulemaking on marketing exclusivity, is similarly misplaced.

The Plain Language of the Statute Contradicts Amphastar's Argument

When the provisions for marketing exclusivity were added to the FDCA, Congress drafted separate provisions to provide exclusivity against section 505(j) and 505(b) applications, respectively. Thus, for products with previously approved active ingredients, three-year exclusivity against 505(j) applications is set forth at FDCA section 505(j)(5)(F)(iii) in the following terms:

> If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of *an application submitted under this subsection [i.e. subsection 505(j)] for the conditions of approval of* such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

See 21 U.S.C. § 355(j)(5)(F)(iii) (emphasis added).

Three-year exclusivity against 505(b)(2) applications is set forth at FDCA section 505(c)(3)(E)(iii), in the following terms:

> If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is

> approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of *an application submitted under subsection (b) of this section* [*i.e.* subsection 505(b)] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section *if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.*

See 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added).

The two statutory sections quoted above are identical except for the italicized language. This is because the two provisions provide identical three-year exclusivity protection -- the only difference being that one section provides exclusivity against ANDAs, while the other provides exclusivity against 505(b)(2) applications.[1]

The clause that Amphastar has focused on -- italicized in the section 505(c)(3)(E)(iii) provision quoted above -- does not mean that exclusivity applies only against applicants that rely on the exclusivity holder's data. Indeed, Amphastar provides no explanation as to how the clause could have that meaning. Rather, this clause serves to indicate that the provision will block approval not of all applications "*submitted under subsection (b) of this section* [subsection 505(b)]," but only of applications in which the "full reports of investigations" that are relied on by the applicant were not conducted by or for the applicant -- that is, applications that are submitted under section 505(b)(2). *See* 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added).[2] In other words, three-year marketing exclusivity will not block the submission of a 505(b)(1) application that contains full reports of safety and effectiveness.

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[1] In the preamble to the proposed rule on marketing exclusivity regulations, FDA recognized that while section 505(j)(5)(F) provides exclusivity against ANDAs (including ANDAs submitted pursuant to suitability petitions), and section 505(c)(3)(E) provides exclusivity against "applications under section 505(b)(2) of the act," the exclusivity protections afforded by the two provisions "are essentially the same." *See* 54 Fed. Reg. 28,872, 28,896 (July 10, 1989).

[2] The terms used to identify 505(b)(2) applications in the final clause of section 505(c)(3)(E)(iii) are identical to the terms used in section 505(b)(2) itself. *See* 21 U.S.C. § 355(b)(2) (defining 505(b)(2) applications as those for which "the investigations described in clause (A) of [section 505(b)(1)] and relied upon by the applicant for approval of the application were not conducted by or for the applicant" and for which "the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted").

The *King Pharmaceuticals* Case Does Not Support Amphastar's Argument

In a further attempt to support its argument that three-year exclusivity under section 505(c)(3)(E)(iii) blocks the approval only of subsequent applications that rely on data originally submitted by the exclusivity holder, *see* Amphastar Comments at 3-4, Amphastar cites the memorandum opinion and order in *King Pharmaceuticals, Inc. et al. v. FDA*, C.A. No. 04-1058 (D.D.C. July 8, 2004) (Memorandum Opinion). In that case, King Pharmaceuticals sought an order requiring FDA to revoke the approval of several supplemental applications that had been filed under section 505(b)(2) by King's competitors. *See* Memorandum Opinion at 1. These competing manufacturers intervened in the case on the side of FDA. *Id.* at 2.

King argued that under FDCA section 505(b)(2)(A), these supplemental applications -- which sought findings of therapeutic equivalence to King's product -- should have contained certifications to King's patent on levothyroxine. *See id.* at 1, 4-5. The court disagreed with King and upheld FDA's approval of the supplemental applications. *Id.* at 13. Specifically, the court held that under section 505(b)(2)(A), a 505(b)(2) applicant need only certify to patents on the drugs that were studied in the safety and effectiveness investigations that the 505(b)(2) applicant relies on for approval. *See* Memorandum Opinion at 10, 13.

Amphastar asserts that the language of section 505(b)(2)(A), which was at issue in *King*, "tracks" the language of the three-year exclusivity provision in section 505(c)(3)(E)(iii). *See* Amphastar Comments at 6. Based on the supposed similarity between the two provisions, Amphastar argues that three-year exclusivity under section 505(c)(3)(E)(iii) should not block the approval of a subsequent application unless the application relies on the exclusivity holder's data. *See id.* ("Similar to the intervenors in *King*, Amphastar did not rely on ISTA's proprietary data, and ISTA's exclusivity cannot bar Amphastar from the marketplace.").

Amphastar is correct that the phrase "and relied upon by the applicant for approval of the application" occurs in both section 505(b)(2) and section 505(c)(3)(E)(iii). Beyond that point, Amphastar's argument from *King* represents a complete misreading of these two statutory sections.

In establishing the patent certification requirement for 505(b)(2) applicants, Section 505(b)(2)(A) explicitly provides that certification is required only for patents claiming the drug "*for which* such investigations were conducted" -- *i.e.*, patents on the drug that was studied in the "full reports of investigations" relied on by the 505(b)(2) applicant. 21 U.S.C. 355(b)(2)(A) (emphasis added). In this provision, the phrase "for which" links the certification requirement to the studies the 505(b)(2) applicant relies on for approval. If a drug is one "*for which*" studies were conducted and the applicant relies on those studies, the applicant must certify to any patents on that drug.

Amphastar appears to be arguing that in the three-year exclusivity provision at section 505(c)(3)(E)(iii), a similar link is established between the scope

of the exclusivity -- the kinds of applications that are blocked -- and the studies the 505(b)(2) applicant relies on for approval. This is not the case. Under section 505(c)(3)(E)(iii), three-year exclusivity will block approval of any 505(b) application in which "the investigations . . . relied upon . . . were not conducted by or for the applicant," provided the application seeks the same "conditions of approval" as the first application.

In support of its interpretation of section 505(c)(3)(E)(iii), Amphastar points again to the final clause of that subsection -- "if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant . . . ." *See* Amphastar Comments at 8 (highlighting language in statute). As explained above in Section A.1, the purpose of this clause is to indicate that section 505(c)(3)(E)(iii) provides exclusivity against 505(b)(2) applications, rather than against 505(b)(1) applications (or against ANDAs, which are covered at section 505(j)(5)(F)(iii)). Amphastar provides no explanation as to how the cited language in section 505(c)(3)(E)(iii) supports its position.

FDA Statements Made In The Preambles To FDA's Marketing Exclusivity Regulations Do Not Support Amphastar's Argument

Amphastar also cites language in the preamble to FDA's proposed rule on marketing exclusivity regulations, in which FDA stated that three-year exclusivity would block the approval "of an ANDA or of a 505(b)(2) application for a duplicate drug product or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) for a similar drug product *that relies on the information supporting the new conditions of approval of the first-approved application*." *See* 54 Fed. Reg. 28,872, 28,899 (July 10, 1989) (emphasis added). According to Amphastar, the italicized language means that no subsequent ANDA or 505(b)(2) application will be blocked unless that application relies on studies conducted by the first-approved applicant. *See* Amphastar Comments at 8 (interpreting the preamble language as "tying reliance on studies to exclusivity").

This interpretation is incorrect. In the quoted passage, FDA was clarifying the treatment of ANDAs submitted pursuant to suitability petitions, as distinct from regular ANDAs. Suitability petitions are a form of ANDA in which applicants can petition FDA for permission to submit an abbreviated application for a drug that "has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug." 21 U.S.C. § 355(j)(2)(C); *see also* 21 C.F.R. § 314.93.

Suitability petitions are not explicitly addressed in the statutory provision that provides three-year exclusivity against ANDAs. *See* 21 U.S.C. § 355(j)(5)(F)(iii) (providing three-year exclusivity against any application "submitted under [FDCA section 505(j)]"). Presumably, that is why FDA sought to clarify the treatment of suitability petition ANDAs in the preamble to the proposed rule on marketing exclusivity.

The italicized language in the passage cited by Amphastar refers not to all applications submitted during the exclusivity period, but only to suitability petition

ANDAs. The meaning of the passage is that while regular ANDAs (and 505(b)(2) applications) will be blocked by three-year exclusivity whenever they seek the same "conditions of approval" as the exclusivity holder, suitability petition ANDAs -- which may not be for the same "conditions of approval," because they differ from the listed drug in specified ways -- are still treated as ANDAs for exclusivity purposes, and will therefore be blocked as long as they rely on "the information supporting the new conditions of approval of the first-approved application." *See* 54 Fed. Reg. 28,872, 28,899; 21 C.F.R. § 314.93(b).

In other words, as FDA has interpreted the statutory provisions on three-year exclusivity, ANDAs submitted pursuant to suitability petitions are a type of ANDA and therefore will be blocked by three-year exclusivity where they rely on the information that supported the first application, even though the "conditions of approval" in a suitability petition application may differ from those of the listed drug.

This interpretation of the preamble language is clearly supported by FDA's regulation defining the scope of three-year exclusivity (against both ANDAs and 505(b)(2)s). Under this regulation, three-year exclusivity blocks the approval of "a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of the original application, *or* an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act *that relies on the information supporting the conditions of approval of an original new drug application*." *See* 21 C.F.R. § 314.108(b)(4)(iv) (emphasis added). It is evident from the wording of this regulation, which matches the wording of the preamble discussed above, that the italicized language applies only to suitability petitions and not to regular ANDAs or 505(b)(2)s.

Other statements made by FDA in the same preamble support ISTA's position that three-year exclusivity blocks all subsequent ANDAs and 505(b)(2)s for the same "conditions of approval" as the first application. For example, FDA stated that

> [t]he exclusivity provisions of sections 505(c)(3)(D)(iii) and (iv) of the act [now sections 505(c)(3)(E)(iii) and (iv)] delay the effective date of approval of *any 505(b)(2) application that is for the conditions of use of a previously approved application that contained new clinical investigations essential for approval*. Consequently, if two 505(b)(2) applications are under review at the same time and one is approved before the other, the effective date of approval of the second application to be approved will be delayed, regardless of the date of submission, if the first contained new clinical investigations essential for approval and thereby qualified for exclusivity.

54 Fed. Reg. 28,872, 28,901(emphasis added).

The Scope Of Three-Year Exclusivity Is Not Defined By The "Purpose" Of The Exclusivity Holder's Studies

Amphastar asserts that "the purpose of the clinical study that justifies the three-year exclusivity should define the scope of that exclusivity." Specifically, Amphastar argues, "ISTA's hypersensitivity clinical study was conducted to demonstrate that ISTA's product was safe. The scope of ISTA's exclusivity is therefore limited to ISTA's formulation." Amphastar Comments at 10.

While this argument is repeated over several pages, *see id.* at 9-11, the only discernable support offered is a citation to *Zeneca, Inc. v. Shalala*, 1999 WL 728104 (D. Md. 1999) (unreported in F.Supp.2d). *See* Amphastar Comments at 10 n.6. Amphastar cites this case for the proposition that three-year exclusivity should block only subsequent applications that seek approval of the same product as the exclusivity holder. *See id.* at 10 ("The scope of ISTA's exclusivity is therefore limited to ISTA's formulation."). Amphastar misreads the holding in *Zeneca*. That case interpreted the scope of exclusivity that attaches to a *supplement* to a 505(b) application. Specifically, under section 505(j)(5)(F)(iv), a supplement containing new clinical investigations receives three years of exclusivity against any 505(j) application that seeks approval of "*a change approved in the supplement*." 21 U.S.C. 355(j)(5)(F)(iv) (emphasis added). Zeneca, the holder of such three-year exclusivity, argued that its exclusivity should have blocked FDA approval of a similar product containing a different preservative. *See Zeneca, Inc. v. Shalala*, 1999 WL 728104 at *7. The "change" approved in Zeneca's supplement, however, related to its own preservative, and not to preservatives in general. *Id.* at *12. Therefore, because Zeneca's exclusivity was granted based on submission of a supplement and attached only to "a change approved in the supplement," the court held that Zeneca's exclusivity could not block the approval of a product containing a different preservative. *Id.*

ISTA's claim of three-year exclusivity is based on its submission of a 505(b)(2) application, not a supplement. The exclusivity awarded to applications and supplements is governed by different statutory provisions. *See* 21 U.S.C. § 355(j)(5)(F)(iii), (iv). Therefore, Amphastar's argument from *Zeneca* is irrelevant.

Three-Year Exclusivity Blocks All ANDAs and 505(b)(2)s For The Same "Conditions of Approval," Not Just Applications That Are For The Same Product As The Exclusivity Holder's

Under the FDCA, three-year exclusivity blocks applications that are for the same "conditions of approval" as the exclusivity holder's application. *See* 21 U.S.C. § 355(c)(3)(E)(iii), (j)(5)(F)(iii). Seeking to narrow the scope of three-year exclusivity, Amphastar asserts that a subsequent application is not for the same "conditions of approval" unless it replicates the application submitted by the exclusivity holder. *See* Amphastar Comments at 14-15. Amphastar essentially takes the position that three-year exclusivity will only block applications that contain the same data as were submitted by the exclusivity holder, and that seek approval of the same specific drug product as the exclusivity holder. *See id.* at 15 (arguing that because Amphastar submitted clinical data on its own product as opposed to clinical data on Vitrase, "the 'conditions of approval' therefore must

have differed between the two products" and Amphastar should not be blocked by Vitrase's three-year exclusivity).

As a threshold matter, the arguments Amphastar uses to support its interpretation of the term "conditions of approval" do not stand up. First, Amphastar cites a passage from the preamble to FDA's proposed rule on marketing exclusivity that describes the types of changes for which three-year exclusivity should be *granted*: "'FDA expects that only those changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use would be granted exclusivity. These are the types of changes in a drug product that require prior approval by FDA before the change may be made.'" *See* Amphastar Comments at 14 (*quoting* 54 Fed. Reg. 28,872, 28,899). This language addresses the *granting* of three-year exclusivity, and has no bearing on the issue of what kinds of applications should be *blocked* by that exclusivity.[3] Second, Amphastar repeats its earlier reference to FDA's preamble statement that three-year exclusivity would block the approval "'of an ANDA or of a 505(b)(2) application for a duplicate drug product or an ANDA submitted pursuant to an approved petition under section 505(j)(2)(C) for a similar drug product *that relies on the information supporting the new conditions of approval of the first-approved application*.'" *See* Amphastar Comments at 15 (*quoting* 54 Fed. Reg. 28,872, 28,899) (emphasis added). This passage does not support Amphastar's interpretation of "conditions of approval." As discussed above in Section A.3, the italicized language is meant to distinguish suitability petition ANDAs from other ANDAs.[4]

More importantly, Amphastar's interpretation is at odds with the statute and with FDA's regulations interpreting the statute. Under FDCA section 505(c)(3)(E)(iii), the class of applications that will be blocked by three-year exclusivity is defined to include any subsequent 505(b)(2) application for the same "conditions of approval" as the exclusivity holder -- whether the subsequent application relies on the exclusivity holder's application or on another application.[5] Under the statute, therefore, the scope of exclusivity protection is

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[3] Even if the types of changes cited by Amphastar did define the term "conditions of approval" -- in other words, even if three-year exclusivity blocked only products with the same "active ingredient(s), strength, dosage form, route of administration [and] conditions of use" as the original applicant -- ISTA's three-year exclusivity in this case would still be effective against any subsequent hyaluronidase injection product for the same indications as Vitrase.

[4] In its block quote citing the passage from the preamble, Amphastar leaves out FDA's reference to suitability petition ANDAs, incorrectly implying that the clause reading "that relies on the information supporting the new conditions of approval of the first-approved application" modifies the words "ANDA" and "505(b)(2) application" rather than "ANDA submitted pursuant to an approved petition under section 505(j)(2)(C)." *See* Amphastar Comments at 15.

[5] This interpretation is consistent with FDA's statements in the rulemaking on marketing exclusivity. The preamble to the proposed rule states that the FDCA provisions on three-year exclusivity "delay the effective date of approval of all ANDAs or 505(b)(2) applications that have the same 'conditions of approval' as

tied to the holder's "conditions of approval" rather than to the application that is referenced by the subsequent applicant. Because of this, the protection offered by three-year exclusivity cannot be limited to applications that contain the same data and seek approval of the same product as the exclusivity holder's. For example, the statute clearly contemplates that a 505(b)(2) application that references the exclusivity holder's application -- an application that by definition would represent a change from the exclusivity holder's product, and would include additional data[6] -- will be blocked by three-year exclusivity if it is for the same "conditions of approval" as the exclusivity holder. A 505(b)(2) that relies on an application other than the exclusivity holder's may also differ from the exclusivity holder's product, and contain different data. Yet if submitted for the same "conditions of approval" as the exclusivity holder, such an application will be blocked by three-year exclusivity.

In the course of a lengthy rulemaking in which FDA made detailed interpretations of many aspects of the marketing exclusivity provisions,[7] the agency did not act in any way to narrow the meaning of "conditions of approval." Instead, FDA retained the term "conditions of approval" without any qualification in its regulations. *See* 21 C.F.R. § 314.108(b)(4)(iv). When those regulations were proposed, FDA received a comment asking that the agency adopt a narrow interpretation of "conditions of approval," so that "subsequent applicants who conduct their own studies to obtain approval [would] not be subject to the original applicant's exclusivity." *See* 59 Fed. Reg. 50,338, 50,359-360 (October 3, 1994) (comment 105); *see also* ISTA Petition at 8-9. FDA declined to adopt this narrow interpretation, acknowledging simply that full NDAs under section 505(b)(1) would not be blocked by three-year exclusivity. 59 Fed. Reg. at 50,360.

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In short, FDCA section 505(c)(3)(E)(iii) cannot be interpreted to mean that a subsequent application must contain the same data as were submitted by the exclusivity holder, and seek approval of the same specific drug product as the exclusivity holder, in order to be for the same "conditions of approval." Under that interpretation, three-year exclusivity would be meaningless for any product

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the innovator's drug, without regard to whether the ANDA 'refers to' the innovator's product or to another version of the same product for which a subsequent new drug application was approved." *See* 54 Fed. Reg. at 28,897 (*quoting* 21 U.S.C. § 355(c)(3)(E)(iii), (j)(5)(F)(iii)). Therefore, FDA stated, three-year exclusivity cannot be interpreted as "covering only specific drug products." *See* 54 Fed. Reg. at *id.*

[6] *See* FDA Guidance, *Applications Covered by Section 505(b)(2)* (October 1999), at 3 ("[a]n applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug").

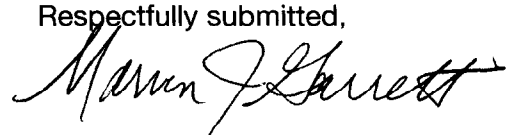
[7] FDA's proposed regulations on marketing exclusivity were issued in 1989, and the regulations were not finalized until 1994. Both the proposed and final rule notices contain extensive interpretation of the statutory provisions on marketing exclusivity. *See generally* 54 Fed. Reg. 28,872 (July 10, 1989) (proposed rule notice); 59 Fed. Reg. 50,338 (October 3, 1994) (final rule notice).

where -- as with hyaluronidase -- FDA has determined that subsequent applications must be supported by clinical data specific to the product at issue.

Specifically, in its response to the citizen petition submitted by Baxter Healthcare Corporation in October 2003, FDA stated that any mammalian-source hyaluronidase -- *i.e.* any hyaluronidase that falls within the USP monograph[8] -- will at a minimum require clinical safety studies for marketing approval. *See* Letter From Steven Galson, FDA CDER to Kent S. Allenby, Baxter Healthcare Corp. (May 5, 2004) (FDA Docket No. 2003P-0494/CP1) (FDA Baxter Response), at 6. For these "monograph" products, effectiveness was established by a DESI review and can be confirmed by means of the USP *in vitro* functional assay test. *See id.* at 3-4. An application submitted for a non-mammalian, "non-monograph" hyaluronidase product would not be covered by the DESI determination and therefore cannot benefit from the same assumptions as mammalian-source products. Such "non-monograph" products presumably would require the submission of clinical data on effectiveness as well. Therefore, a variety of different applications for hyaluronidase products could be submitted to FDA under section 505(b)(2),[9] each of which might need to be supported by a different kind of data.

Under the statutes and regulations governing three-year exclusivity, however, there is no basis for treating any of these subsequent applications differently from any other. To the extent each of these subsequent 505(b)(2) applications seeks approval of a hyaluronidase injection product for the same indications as Vitrase, it is for the same "conditions of approval" as Vitrase and should be blocked by Vitrase's three-year exclusivity.

Respectfully submitted,



Marvin J. Garrett
Vice President, Regulatory
Affairs and Quality Assurance
& Compliance
ISTA Pharmaceuticals, Inc.

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[8] *See* USP Official Monographs, Hyaluronidase Injection and Hyaluronidase for Injection, USP 28 NF 23 (January 1, 2005).

[9] Depending on the nature of clinical data required, some applications -- particularly those for non-monograph products -- may require submission of a 505(b)(1) application.

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662 6291
WWW COV COM

WASHINGTON
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GRAIL WALSH SIPES
TEL 202.662.5379
FAX 202.778.5379
GSIPES@COV.COM

August 25, 2005

BY HAND DELIVERY

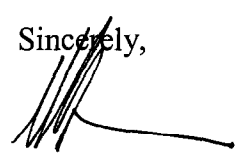
Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
Room 1061, 5630 Fishers Lane
Rockville, MD 20852

Re: FDA Docket No. 05P-0134

Dear Sir or Madam:

Enclosed for filing is the original and one copy of a comment to be submitted to the above-named docket.

Sincerely,



Grail Sipes

Enclosures